What is claimed is:

1. A method for treating atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an aP2 inhibitor.

2. The method as defined in Claim 1 wherein the aP2 inhibitor binds to the aP2 protein and inhibits its function and/or its ability to bind free fatty acids.

3. The method as defined in Claim 1 wherein the aP2 inhibitor contains a hydrogen bond donator or acceptor group and interacts directly or through an intervening water molecule either by ionic or hydrogen bonding interactions, with one, two, or three of the three amino acid residues, designated as Arg 106, Arg 126 and Tyr 128 in human aP2 within the aP2 protein.

4. The method as defined in Claim 3 wherein the hydrogen bond donator or acceptor group is acid in nature.

5. The method as defined in Claim 3 where said aP2 inhibitor contains an additional substituent which binds to (in) and/or interacts with a discrete pocket within the aP2 protein defined roughly by the amino acid residues Phe 16, Tyr 19, Met 20, Val 23, Val 25, Ala 33, Phe 57, Thr 74, Ala 75, Asp 76, Arg 78 in human aP2.

6. The method as defined in Claim 5 wherein said additional substituent in said aP2 inhibitor is hydrophobic in nature.

7. The method as defined in Claim 5 in which the through space distance from the hydrogen bond donor/acceptor group and the additional substituent group in said aP2 inhibitor is within the distance of about 7 to about 15 Angstroms.

8. The method as defined in Claim 1 wherein Type II diabetes is treated.

9. The method as defined in Claim 1 wherein the aP2 inhibitor is employed in the form of a pharmaceutically acceptable salt thereof or a prodrug ester thereof.

10. The method as defined in Claim 1 wherein the aP2 inhibitor includes an oxazole or analogous ring, a pyrimidine derivative or a pyridazinone derivative.

11. The method as defined in Claim 10 wherein the aP2 inhibitor is a substituted benzoyl or biphenyl-2-oxazole-alkanoic acid derivative, an oxazole derivative, a 2-thio-4,5-diphenyloxazole S-derivative, a phenyl-heterocyclic oxazole derivative, a diaryloxazole derivative, a 4,5-diphenyloxazole derivative, an oxazole carboxylic acid derivative, a phenyloxazolyloxazole derivative, or a 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acid derivative.

12. The method as defined in Claim 10 wherein the aP2 inhibitor is a 2-benzyloxypyrimidine derivative, a dihydro(alkylthio)(naphthylmethyl)oxypyrimidine derivative, a thiouracil derivative, or an α-substituted pyrimidine-thioalkyl or alkyl ether derivative.

13. The method as defined in Claim 10 wherein the aP2 inhibitor is a pyridazinone acetic acid derivative.

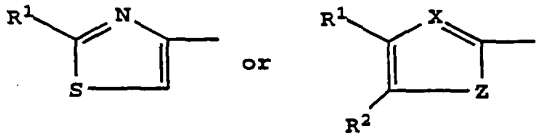
14. The method as defined in Claim 10 wherein the aP2 inhibitor is

(I)a substituted benzoylbenzene or biphenyl alkanoic acid derivative having the structure:

I $A(CH_2)_nO-B$

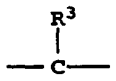
wherein

A is a group having the formula



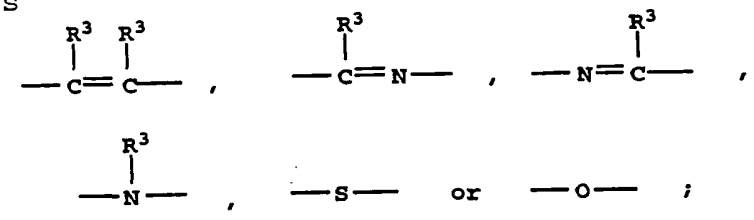
wherein

X is -N- or



;

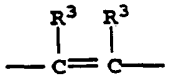
Z is



R^1 is hydrogen, lower alkyl or phenyl;

R^2 is hydrogen or lower alkyl; or

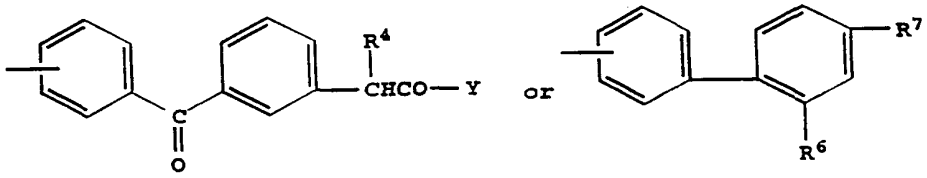
R^1 and R^2 taken together form a benzene ring, with the proviso that when X is -N-, Z is other than



R^3 is hydrogen or lower alkyl;

n is 1-2;

B is



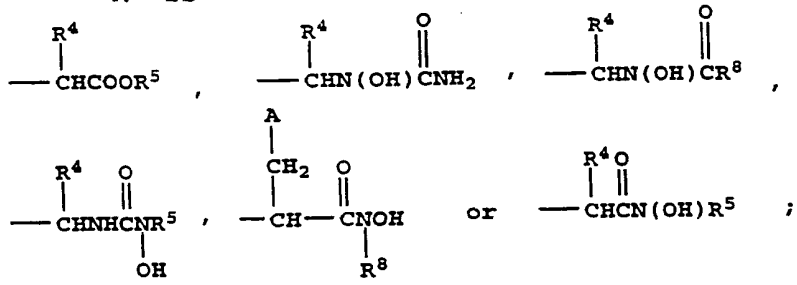
wherein

Y is OR^5 or N(OH)R^8;

R^4 and R^5 are each, independently, hydrogen or lower alkyl;

R^6 is hydrogen, halo or nitro;

R^7 is



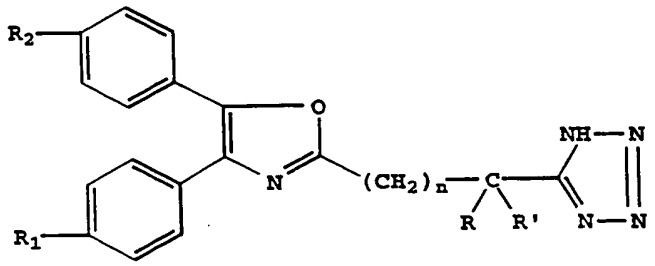
R^8 is lower alkyl;

m is 0-3;

or a pharmacologically acceptable salts thereof;

(II) oxazole derivatives which have the structure

II



in which;

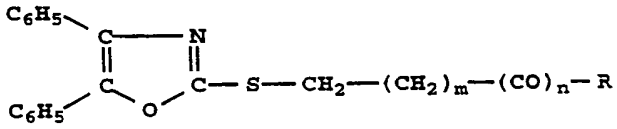
R and R' are identical or different and represent a hydrogen atom or an alkyl radical containing 1 or 2 carbon atoms,

R_1 and R_2 are identical or different and represent hydrogen or halogen atoms or alkyloxy radicals in which the alkyl portion contains 1 to 4 carbon atoms in a straight or branched chain, and

n equals 3 to 6, as well to their salts;

(III) 2-thiol-4,5-diphenyloxazole S-derivatives which have the structure

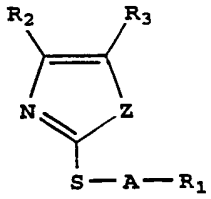
III



wherein m is 0, 1 or 2, n is 1 and R represents hydroxy, alkoxy or amino, and pharmaceutically acceptable addition salts thereof;

(IV) azole derivatives of the structure

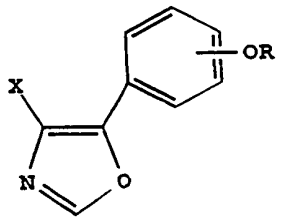
IV

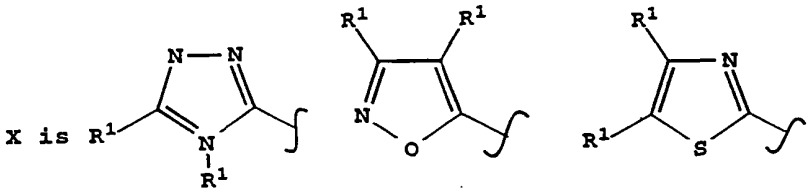


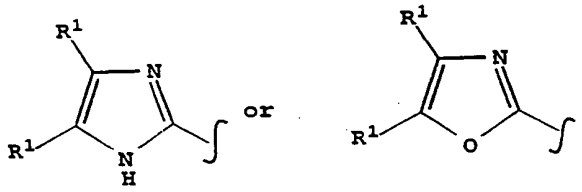
wherein R_1 is carboxyl, esterified carboxyl or other functionally modified carboxyl group; R_2 and R_3 each are aryl of up to 10 carbon atoms; A is C_nH_{2n} in which n is an integer from 1 to 10, inclusive; and Z is O or S, and physiologically acceptable salts thereof;

(V) phenyl-heterocyclic oxazole derivatives which have the structure

V



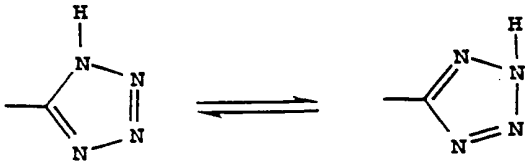




R is CH_2R^2;

R^1 is Ph or Th;

R^2 is



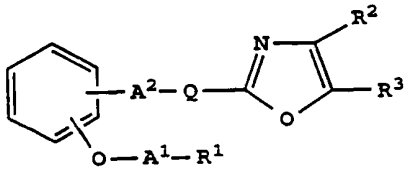
CO_2R^3; and

R^3 is H, or C_1-C_4 lower alkyl;

or pharmaceutically acceptable salt thereof;

(VI) diaryloxazole derivatives having the structure

VI



wherein R^1 is carboxy or protected carboxy,

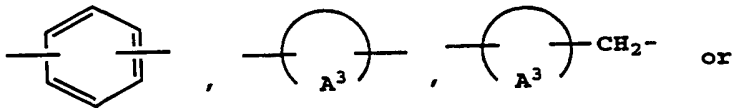
R^2 is aryl,

R^3 is aryl,

A^1 is lower alkylene,

A^2 is bond or lower alkylene and

-Q- is

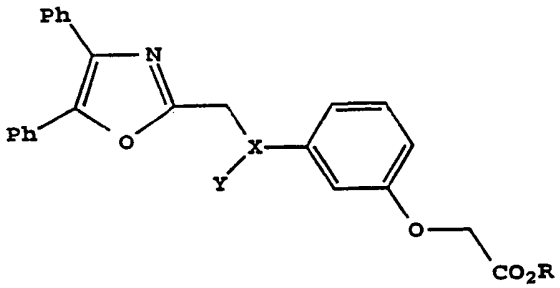


(in which  is cyclo (lower)alkane or cycle(lower)alkene,

each of which may have suitable substituent(s));

(VII) 4,5-diphenyloxazole derivatives having the structure

VIIA



wherein

R is H or C_1-C_5 lower alkyl,

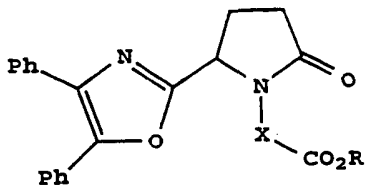
X is N or CH,

Y is H or CO_2R^1, or COR^2, provided that when X is CH, Y is not H,

R^1 is C_1-C_5 lower alkyl, or phenylmethyl, and

R^2 is C_1-C_5 alkyl;

VIIB



wherein

R is H or C_1-C_5 lower alkyl,

X is $(CH_2)_n$ or para or meta substituted phenyl wherein the substituent is OR^2,

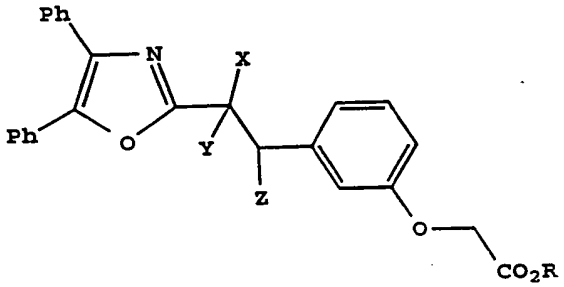
R^2 is C_1-C_5 alkyl, and

n is an integer of 4 to 8,

and pharmaceutically acceptable salts thereof;

(VIII) oxazole carboxylic acid derivatives having the structure

VIII



wherein

Y and Z are independently hydrogen or together form a bond;

X is CN, CO_2R^1 or $CONR^2R^3$;

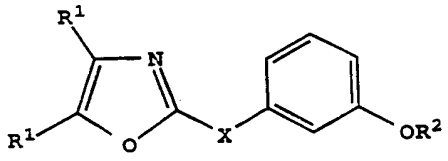
R and R^1 are independently or together H, Na, or C_1-C_5 lower alkyl;

R^2 and R^3 are independently or together H, or C_1-C_5 lower alkyl;

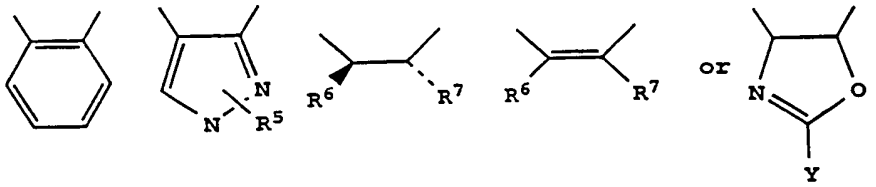
or alkali metal salt thereof;

(IX) phenyloxazolyloxazole derivatives having the structure

IX



wherein

X is 

Y is CH_3, Ph, or OH, provided that when Y is OH, the compound exists in the keto-enol tautaumerism form

R^1 is Ph or Th;

R^2 is CH_2R^3;

R^3 is CO_2R^4;

R^4 is H or C_1-C_5 lower alkyl;

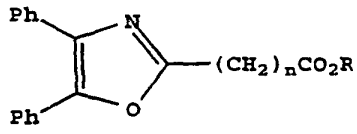
R^5 is H or CH_3; R^6 is OHCHN or H_2N; and

R^7 is H or OH;

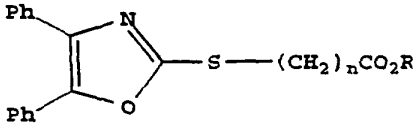
or pharmaceutically acceptable salt thereof;

(X) 2-(4,5-diaryl)-2-oxazolyl substituted phenoxyalkanoic acids and esters having the strucutre

XA

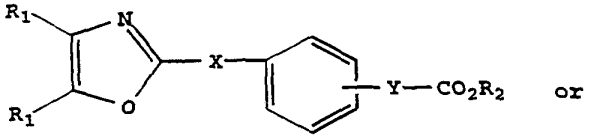


XB



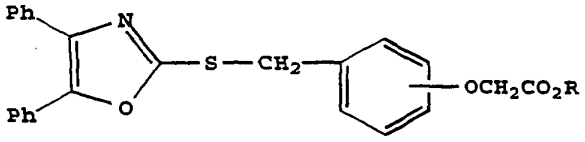
(wherein n is 7-9 and R is hydrogen or lower alkyl; or when R is hydrogen, the alkali metal salt thereof),

XC



or

XD



wherein

R_1 is phenyl or thienyl;

R_2 is hydrogen, lower alkyl or together with CO_2 is tetrazol-1-yl;

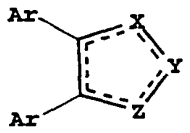
X is a divalent connecting group selected from the group consisting of CH_2CH_2, CH=CH, and CH_2O;

Y is a divalent connecting group attached to the 3- or 4-phenyl position selected from the group consisting of OCH_2, CH_2CH_2 and CH=CH,

or when R_2 is hydrogen, an alkali metal salt thereof;

(XI) substituted 4,5-diaryl heterocycles having the formula

XI



in which

each group Ar is the same or different and is optionally substituted phenyl or optionally substituted heteroaryl;

X is nitrogen or CR^1;

Y is nitrogen, $N(CH_2)_nA$ or $C(CH_2)_nA$;

Z is nitrogen, oxygen or $N(CH_2)_nA$, and the dotted line indicates the optional presence of a double bond so as to form a fully unsaturated heterocyclic ring;

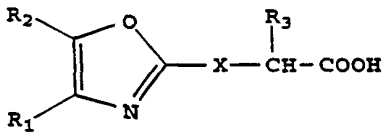
R^1 is hydrogen, C_{1-4}alkyl, optionally substituted phenyl or optionally substituted heteroaryl;

n is 4 to 12; and

A is CO_2H or a group hydrolysable to CO_2H, 5-tetrazolyl, SO_3H, $P(O)(OR)_2$, $P(O)(OH)_2$, or P(O)(R)(OR) in which R is hydrogen or C_{1-4}alkyl, or a pharmaceutically acceptable salt thereof;

(XII) compounds which have the structure

XII



Where X is O or S;

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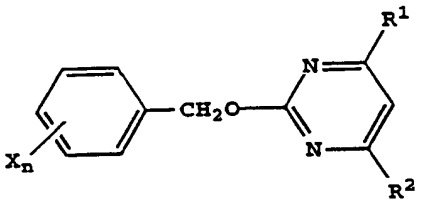
R_1 is H, phenyl or phenyl substituted with F, Cl or Br or alkoxy,

R_2 is H, alkyl, phenyl or phenyl substituted with F, Cl or Br or alkoxy, and

R_3 is H or alkyl;

(XIII) 2-benzyloxypyrimidine derivatives having the following structure

XIII



wherein

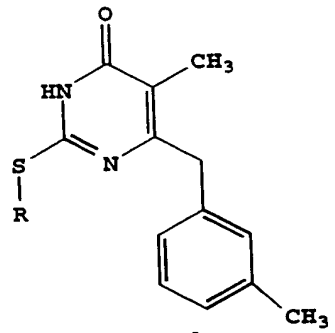
R^1 and R^2 are each independently H, a halogen, hydroxyl, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_5 alkenyl, C_3-C_5 alkynyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_3-C_5 alkenyloxy, C_3-C_5 alkynyloxy, C_1-C_4 alkylthio, or phenyl, with the proviso that at least one of R^1 and R^2 must be hydroxyl;

n is an integer of 0 to 5; and

each X which may be identical or different if n is greater than 1, is a halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_7-C_9 aralkyloxy, phenyl, hydroxymethyl, hydroxycarbonyl, C_1-C_4 alkoxycarbonyl, or nitro;

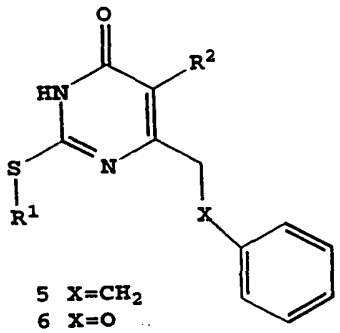
(XIV) dihydro(alkylthio)-(naphthylmethyl)-oxopyrimidines which have the structures

XIVA



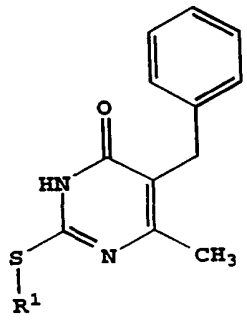
3a R=sec-butyl
3b R=cyclopentyl
3c R=cyclohexyl

XIVB

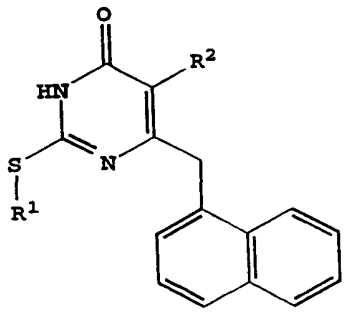


5 $X=CH_2$
6 X=O
7 X=S

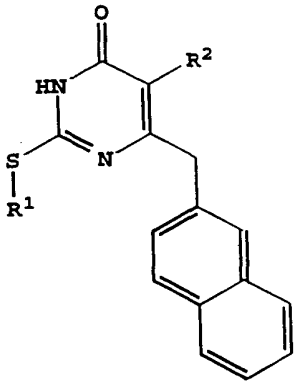
XIVC



XIVD



XIVE



R^1 = sec-butyl, cyclopentyl, cyclohexyl;
R^2 = H, CH_3, including tautomers of the above;

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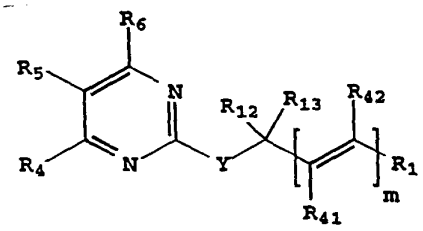
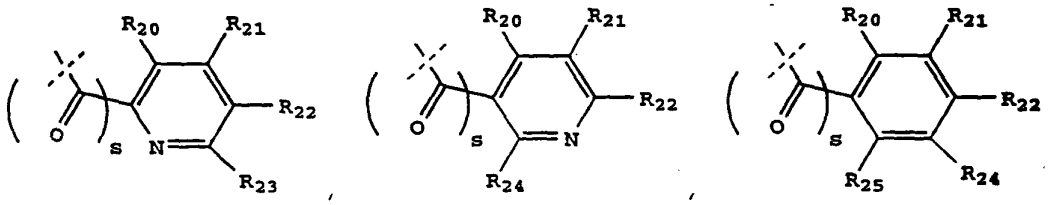
(XVI) α-substituted pyrimidine-thioalkyl and alkylether compounds which have the structure

XVI



where m is 0 or 1;

R^1 is selected from $-CO_2R_{53}$, $-CONR_{54}R_{55}$,



where s is 0 or 1, and R_{20}, R_{21}, R_{22}, R_{23}, R_{24}, and R_{25} are the same or different and are selected from -H, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_3-C_8 cycloalkyl, $-CF_3$, $-NO_2$, -halo, -OH, -CN, phenyl, phenylthio, -styryl, $-CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C(OH)(R_{31}(R_{33})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $(CH_2)_nN(R_{31})(SO_2(R_{33}))$, or where R_{20} and R_{21}, or R_{21} and R_{22}, or R_{22} and R_{23} are taken together to form a five or six-membered saturated or unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C_1-C_6 alkyl, C_1-C_6 alkoxy, -OH, $-CH_2OH$, $-(CH_2)_n-N(R_{31})(R_{32})$, $-C_3$-C_8 cycloalkyl, $-CF_3$, -halo, $CO_2(R_{31})$, $-CON(R_{31})(R_{32})$, $-CO(R_{31})$, $-(CH_2)_nN(R_{31})(CO(R_{33}))$, $-(CH_2)_nN(R_{31})(SO_2(R_{33}))$, -CN, $-CH_2CF_3$ or $-CH(CF_3)_2$, or phenyl and the saturated ring may be optionally substituted with 1, 2 or 3, $-C_1$-C_6 alkyl, $-C_1$-C_6 alkoxy, -OH, $-CH_2OH$ or $-(CH_2)_n-N(R_{31})(R_{32})$ or one oxo (=O);

where n is 0-3 and R_{31}, R_{32} and R_{33} are the same or different and are selected from

-H,

C_1-C_6 alkyl,

phenyl optionally substituted with 1, 2 or 3 -halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CF_3, -OH or -CN,

or where R_{31} and R_{32} taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C_1-C_6alkyl)piperazinyl, or a member selected from

1-cyclohexenyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-imidazolyl, 4-imidazolyl, 2-benzothiazolyl, 2-benzoxazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 2-thiazolyl, 3-isoxazolyl, 5-isoxazolyl, 5-methyl-3-isoxazolyl, 5-phenyl-3-isoxazolyl, 4-thiazolyl, 3-methyl-2-pyrazinyl, 5-methyl-2-pyrazinyl, 6-methyl-2-pyrazinyl, 5-chloro-2-thienyl, 3-furyl, benzofuran-2-yl, benzothien-2-yl, 2H-1-benzopyran-3-yl, 2,3-dihydrobenzopyran-5-yl, 1-methylimidazol-2-yl, quinoxalin-2-yl, piperon-5-yl, 4,7-dichlorobenzoxazol-2-yl, 4,6-dimethylpyrimidin-2-yl, 4-methylpyrimidin-2-yl, 2,4-dimethylpyrimidin-6-yl, 2-methylpyrimidin-4-yl, 4-methylpyrimidin-6-yl, 6-chloropiperon-5-yl, 5-chloroimidazol[1,2-a]pyridin-2-yl, 1-H-inden-3-yl, 1-H-2-methyl-inden-2-yl, 3,4-dihydronaphth-1-yl, S-4-isopropenylcyclohexen-1-yl or 4-dihydronaphth-2-yl;

where R_{53} is selected from -H, C_1-C_6alkyl, C_3-C_6cycloalkyl, phenyl (optionally substituted with 1, 2, or 3 -halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CF_3, -OH, -CN), or a five or six-membered unsaturated ring containing 0 or 1 oxygen, nitrogen or sulfur, where the unsaturated ring may be optionally substituted with -H, C_1-C_6 alkyl, C_1-C_6 alkoxy, -OH, -CH_2OH, or -$(CH_2)_n$-N(R_{31})(R_{32});

where R_{54} and R_{55} being the same or different are selected from -H, C_1-C_6 alkyl, allyl, or phenyl (optionally substituted with 1, 2 or 3 -halo, C_1-C_6 alkyl, C_1-C_6 alkoxy or -CF_3), or taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, -4-(1-C_1-C_6alkyl)piperazinyl;

R_{41} and R_{42}, being the same or different, are selected from -H and C_1-C_4 alkyl;

R_{12} is selected from -H, C_1-C_6 alkyl, -C_3-C_6 ,cycloalkyl, -CN, -C(O)NH_2, -C(O)N(C_1-C_6alkyl)(C_1-C_6alkyl), -CO_2H, -CO_2(C_1-C_6alkyl), -CH_2OH, -CH_2NH_2 or -CF_3;

R_{13} is selected from -H, C_1-C_6 alkyl or -CF_3;

Y is selected from -S-, -S(O)-, -S(O)$_2$, or -O-;

R_4 is -OH;

R_5 is selected -H, -C_2H_4OH, -C_2H_4-O-TBDMS, halo, -C_3-C_6 cycloalkyl, C_1-C_3 alkoxy, -CH_2CH_2Cl or C_1-C_4 alkyl, with the proviso that R_5 is not isobutyl;

or, when R_6 is hydroxyl, R_4 and R_5 are taken together to form a five or six-memebered saturated or unsaturated ring which together with the pyrimidine ring form the group consisting of 7H-pyrrolo[2,3-d]pyrimidine, 5,6-dihydro-7H-pyrrolo[2,3-d]pyrimidine, furo[2,3-d]pyrimidine, 5,6-dihydro-furo[2,3-d]pyrimidine, thieno[2,3-d]pyrimidine, 5,6-dihydro-thieno[2,3-d]pyrimidine, 1H-pyrazolo[3,4-d]pyrimidine, 1H-purine, pyrimido[4,5-d]pyrimidine, pteridine, pyrido[2,3-d]pyrimidine, or quinazoline, where the unsaturated ring may be optionally substituted with 1, 2 or 3, C_1-C_6 alkyl C_1-C_6 alkoxy, -OH, -CH_2OH, or -$(CH_2)_n$-N(R_{31})(R_{32}), -C_3-C_8 cycloalkyl, -CF_3, -halo, -CO_2(R_{31}), -CON(R_{31})(R_{32}), -CO(R_{31}), -$(CH_2)_n$N(R_{31})(CO(R_{33})), -$(CH_2)_n$N(R_{31})(SO_2(R_{33})), and the saturated ring may be optionally substituted with 1, 2 or 3, -C_1-C_6 alkyl, C_1-C_6 alkoxy, -OH, -CH_2OH, or -$(CH_2)_n$-N(R_{31})(R_{32}) or one oxo (=O); and

R_6 is selected from -H, -OH, halo, -CN, -CF_3, -CO_2(R_{61}), -C(O)R_{61} or -C(O)N(R_{61})(R_{62}) where R_{61} and R_{62} are the same or different and are selected from

-H,

C_1-C_6 alkyl,

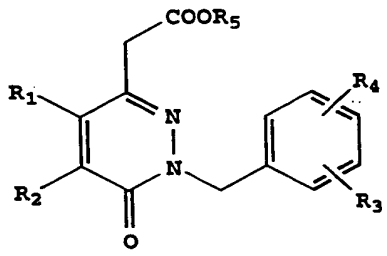
phenyl optionally substituted with 1, 2 or 3 -halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CF_3, -OH, -CN,

or where R_{61} and R_{62} taken together with the attached nitrogen to form a ring selected from -pyrrolidinyl, -

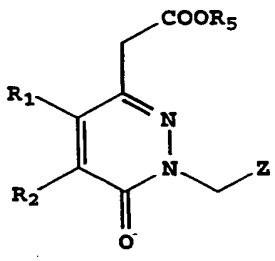
piperidinyl, -4-morpholinyl, -4-thiomorpholinyl, -4-piperazinyl, or -4-(C_1-C_6 alkyl)piperazinyl;

pharmaceutically acceptable salts, hydrates, N-oxides and solvates thereof;

(XVII) compounds which have the structure



XVIIA



XVIIB

where R_1 and R_2 are H, alkyl, aryl or arylalkyl, where the alkyl can include as substituents halogen, CF_3, CH_3O, CH_3S, NO_2, or R_1 and R_2 with the carbons to which they are attached can form methylenedioxy, or

R_1 and R_2 can form a C_3-C_7 non-aromatic ring, or a heterocycle which can be pyridine, pyrazine, pyrimidine, pyridazine, indol, or pyrazole, or an oxygen containing heterocycle which can be pyran or furan, or a sulfur containing heterocycle which can be thiopyran, or thiophene; the heterocycles being optionally substituted with halogen or alkyl,

R_3 and R_4 are H, alkyl, halogen, CF_3, CH_3O, CH_3S or NO_2 or R_3 and R_4 with the carbons to which they are attached can form a methylenedioxy group,

R_5 is H, and

Z is a heterocycle which can be pyridine, thiazole, benzothiazole, benzimidazole or quinoline, which Z group can optionally be substituted with halogen or alkyl.

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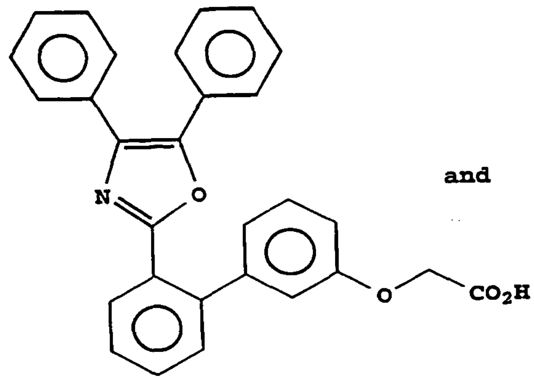
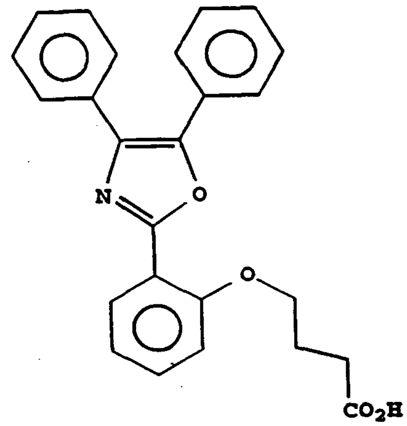
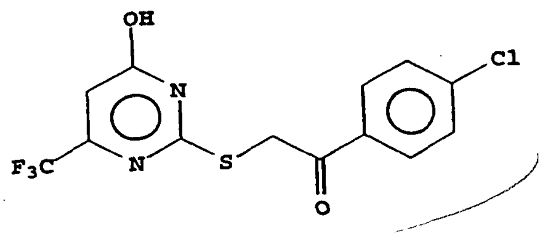
15. The method as defined in Claim 1 wherein the aP2 inhibitor has the structure



and





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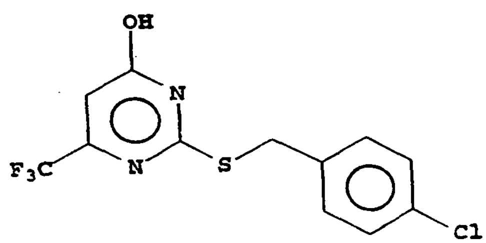

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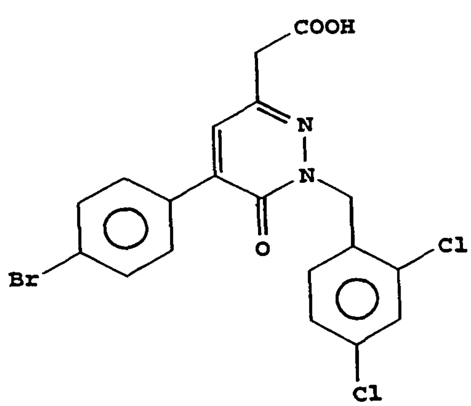

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16. A pharmaceutical combination comprising an aP2 inhibitor and another type antiatherosclerotic agent.

17. The combination as defined in Claim 16 wherien the other antiatherosclerotic agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, other cholesterol lowering agent, a lipoxygenase inhibitor, an ACAT inhibitor or a PPAR α/γ dual agonist.

18. The combination as defined in Claim 16 wherien the antiatherosclerotic agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin or fluvastatin.

19. The combination as defined in Claim 16 wherein the aP2 inhibitor is present in a weight ratio to the antiatherosclerotic agent within the range from about 0.01 to about 100:1.

20. A method for treating atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination as defined in Claim 16.

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